SRD5A3-CDG: Emerging phenotypic features of an ultra-rare CDG subtype

**INTRODUCTION & BACKGROUND**

Congenital disorders of glycosylation (CDGs) are genetic diseases with an extremely broad spectrum of clinical presentations. They are due to defective glycosylation of glyco-proteins or glycolipids and the genetic defects affect several glycosylation pathways.

SRD5A3-CDG (CDG-Iq) is a rare N-glycosylation defect due to steroid 5 alpha reductase type 3 deficiency. Key feature is an early severe visual impairment with variable ocular anomalies often leading to diagnosis. Additional features are still ill defined. In this case study we discuss eleven genetically confirmed cases and report on emerging features involving other systems apart from the eye phenotype.

**METHODS**

Eleven SRD5A3-CDG patients of five sets of sibships were included in the study. Data on nine of eleven patients are yet unpublished. Patients’ results on biochemical and genetic investigations and on in depth phenotyping are presented.

**DEMOGRAPHICS**

A total of 11 patients with SRD5A3-CDG are included in our cohort, with a female to male ratio of 8:3. Current age ranges from 5 to 23 years.

Figure 2 shows the frequency of symptoms seen in our cohort.

**AFFILIATIONS**

1. Metabolic Department, Great Ormond Street Hospital London / UK
2. Institute for Child Health, NIHR Biomedical Research Center (BRC), University College London/UK
3. Department of Ophthalmology, Great Ormond Street Hospital, 4. Department of Radiology, GOSH
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Examples of skin changes seen in SRD5A3-CDG. (A) Well demarcated erythematous, scaly plaque classical of psoriasis seen in patient.

Excessively dry scaly skin representative of ichthyosis seen in patient 1-2 who was born as a collodion baby.

The clinical spectrum of SRD5A3-CDG is still evolving and diagnosis of patients are often only established by untargeted extended mutational screening. All our patients were diagnosed by non-targeted whole exome sequencing and/ or via the 100,000 genome project. There is an apparent phenotypic variability in the clinical features amongst patients with SRD5A3-CDG. This variability interestingly extends to affected siblings within the same families, carrying the same genetic mutation as we could show in our patients’ cohort.

Ophthalmological findings in SRD5A3-CDG have been well characterised. Each of our patients in this series was affected either by nystagmus, retinal dystrophy, optic nerve hypoplasia, squint and / or colobomas. Reviewing our cohort, and those described in the literature, we can suggest that nystagmus followed by the development of early retinal dystrophy and visual impairment forms part of the natural disease history in SRD5A3-CDG patients. Global developmental delay and learning difficulties are a known feature of SRD5A3-CDG, with each of our patients affected to some degree. Overall, SRD5A3-CDG manifests on a wide range of organs, which is likely to reflect the fact that SRD5A3 gene mutations not only affect N- glycosylation but also other glycosylation pathways.

REFERENCES

Neerja Gupta1, Aet al- case of SRD5A3-congenital disorder of glycosylation (CDG1Q) by exome sequencing. Indian J Med Res 147, April 2018, pp 422-426
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**Figure 7: Ophthalmological findings**

MRI of patient 1-2 at age 15 years shows A) thick corpus callosum and mild cerebellar hypoplasia, B) small basal ganglia, C) cavum septum pellucidum et vergae (arrow) and D) non-specific punctate white matter lesions on fluid-attenuated inversion recovery (FLAIR) sequences (arrow). Patient 3-2 scanned at 12 months of age shows retro cerebellar cyst and thin cervical cord, B) signal change of the genu of corpus callosum (immature myelin, black arrow) and small lentiform nucleus, C) mal rotation of hippocampi and D) asymmetry of the globes, more prominent on follow-up (lower image). Patient 4-3 at 7 months of age shows A) small cerebellum and pons and drooping splenium, B) microcephaly with volume loss of the white matter, delayed myelination and volume loss of the lentiform nucleus, C) malrotation of hippocampi and D) volume loss of the optic nerves.

**CONCLUSION**

Key diagnostic features of SRD5A3-CDG are ophthalmological abnormalities with early onset such as retinitis pigmentosa, retinal dystrophy and optic nerve hypoplasia. However, SRD5A3-CDG is a multi-systemic disorder also characterized by variable neurological symptoms including intellectual disability, hypotonia and ataxia. In addition, we demonstrate the presence of cutaneous lesions, as well as spinal, cardiac and endocrine involvement. In our study population new emerging clinical features include dystonia, anxiety disorder, gastrointestinal symptoms and MRI findings of small basal ganglia and mal-rotated hippocampus. The detailed description of the phenotype of this large cohort of patients with SRD5A3-CDG highlights, that the key clinical diagnostic features of SRD5A3-CDG are an early onset of ophthalmological problems in patients with a multisystem disorder with variable symptoms evolving over time. This should aid earlier diagnosis and confirms the need for long-time follow up of patients.

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